(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 August 2003 (28.08.2003)

PCT

(10) International Publication Number
WO 03/070745 A2

(51) International Patent Classification[7]: C07J 43/00, A61K 31/573, 31/58, A61P 5/44, C07J 41/00, 71/00, 5/00

(21) International Application Number: PCT/US03/04655

(22) International Filing Date: 18 February 2003 (18.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/358,246 20 February 2002 (20.02.2002) US
60/428,180 21 November 2002 (21.11.2002) US

(71) Applicant *(for all designated States except US)*: SEPRACOR INC. [US/US]; 84 Waterford Drive, Marlborough, MA 01752 (US).

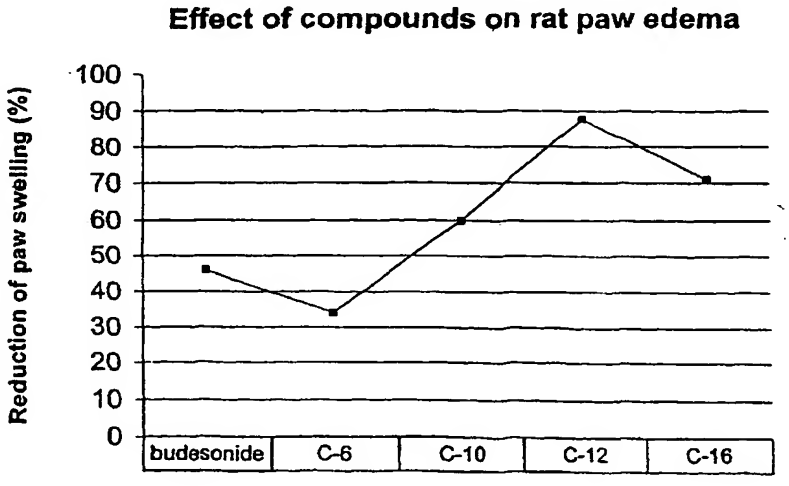
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: GROVER, Paul [US/US]; 4 Warwick Road, Franklin, MA 02038 (US). JONES, Steve [US/US]; 10 Ragged Hill Road, Milford, MA 01757 (US). SENANAYAKE, Chris, H. [US/US]; 12 Isabel's Way, Brookfield, CT 06804 (US). CURRIE, Mark, G. [US/US]; 18 Hall Avenue, Sterling, MA 01564 (US). FANG, Q., Kevin [US/US]; 35 Atwood Street, Wellesley, MA 02181 (US).

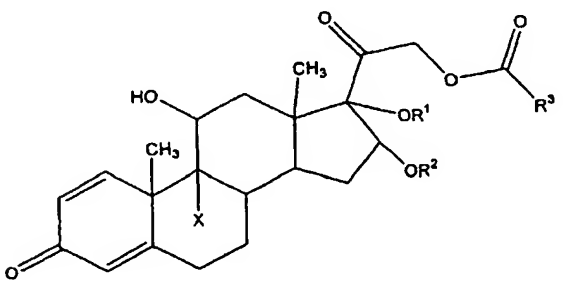
(74) Agent: HANSEN, Philip E.; HESLIN ROTHENBERG FARLEY & MESITI P.C., 5 Columbia Circle, Albany, NY 12203 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

[Continued on next page]

(54) Title: CARBONATE AND CARBAMATE MODIFIED FORMS OF GLUCOCORTICOIDS





(I)

(57) Abstract: Carbonates and carbamates of the formula and related steroid carbonates and carbamates are disclosed. The compounds are useful for treating rhinitis and asthma, particularly by inhalation, and for treating inflammation, particularly by local or topical administration.

WO 03/070745 A2

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

CARBONATE AND CARBAMATE MODIFIED FORMS OF GLUCOCORTICOIDS

Field of the Invention

[0001] The invention relates to antiasthmatic carbonate and carbamate derivatives of glucocorticoids.

Background of the Invention

[0002] Glucocorticoids, in topical, oral and inhaled formulations, are useful for their anti-inflammatory and immunosuppressive activities. Notwithstanding the sophistication of many formulations, many glucocorticoids exhibit significant side-effects that prevent realization of their maximum pharmacologic value. These side-effects stem, in part, from the difficulty of effectively delivering the glucocorticoid drug to a target tissue without increasing systemic concentrations of the drug.

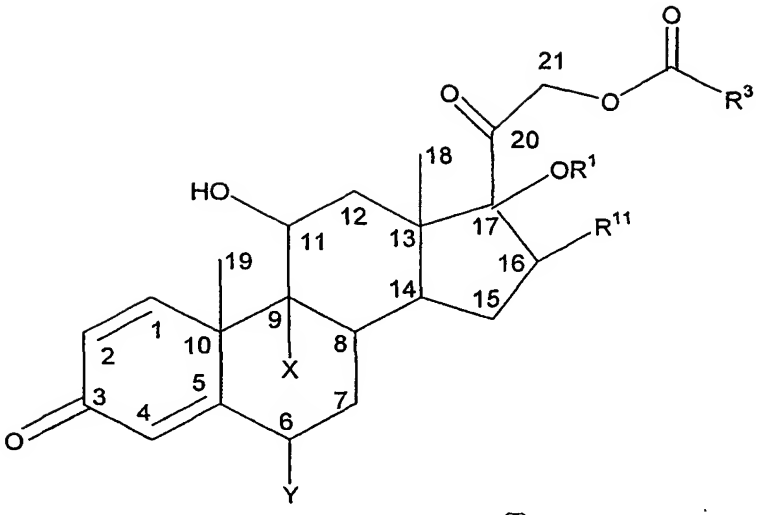
[0003] Inhaled glucocorticoids are an effective therapy for the control of asthma, and improvement with steroids is one of the hallmarks of asthma [Barnes, PJ (1998) in *Asthma: Basic Mechanisms and Clinical Management (3rd ed)*]. The inhaled glucocorticoids work to reduce the inflammation in either lungs, *e.g.* for asthma, or nose, *e.g.* for nasal allergies. Inhaled glucocorticoids are most often administered using a metered dose inhaler (MDI). In the best of circumstances, in controlled clinical settings, only around 30% of the administered dose gets into the lungs. In the general patient population probably only 10% or so of the dose gets into the lungs due to improper use of the inhaler. The rest of the administered drug is deposited in the throat and upper airways, or is swallowed. The drug that is deposited in the throat is responsible for some side effects seen with inhaled glucocorticoids (cough, oropharyngeal candidiasis and dysphonia). For early generation inhaled glucocorticoids, the swallowed drug leads to the same side effects seen

with oral glucocorticoids. In light of the tremendous efficacy of inhaled glucocorticoids in asthma, much effort has gone into reducing the side effects from their use. Although newer glucocorticoids (e.g. budesonide, ciclesonide, triamcinolone and fluticasone) exhibit reduced systemic side effects from swallowed drug - being either poorly absorbed in the gut or subject to extensive inactivation in the liver - they nonetheless display systemic side effects as a result of absorption from the lung into the systemic circulation. The side effects include decreased bone density (Israel, E *et al.*, (2001), *New England Journal of Medicine* 345:941-947 and Wong, CA *et al.*, (2000) *Lancet* 355:1399-1403), which has been correlated with increased risk of fracture. Thus the need still exists for inhaled glucocorticoids with reduced systemic effects.

[0004] Several approaches have been suggested to reduce systemic effects. One such approach takes advantage of inactive prodrugs that are activated in the lung tissues. For example, Dietzel *et al.* [Prog. Respir Res. 31, 91-93 (2001)] have described an isopropyl group esterified at the 21 position of the glucocorticoid core structure. Another approach that has been suggested is the formulation of a glucocorticoid as a liposome. Axelsson *et al.* in a series of US patents (4,693,999; 5,614,514 and 5,888,995) describe selected glucocorticoids modified for formulation into liposomes by esterification at the 21 position with saturated and mono-unsaturated fatty acids with chain lengths up to 20 carbons.

Summary of the Invention

It has now been found that carbonates and carbamates of Formula I:



(I)

provide unexpectedly greater potency for an extended time than do either the parent alcohols or the shorter chain carbonates and carbamates. In the compounds of formula I according to the invention:

R^1 and R^2, independently for each occurrence, represent a hydrogen, lower alkyl or lower acyl, or taken together R^1 and R^2 form a substituted or unsubstituted ketal;

R^3 is $-OR^4$ or $-NR^5R^6$;

R^4 is chosen from C_7 to C_{24} hydrocarbon, -(C_7 to C_{24} hydrocarbon)-COOH and -(C_7 to C_{24} hydrocarbon)-NR^9R^{10};

R^5 is hydrogen or C_7 to C_{24} hydrocarbon;

R^6 is chosen from C_7 to C_{24} hydrocarbon and -(C_7 to C_{24} hydrocarbon)-COOH;

R^9 is hydrogen or C_1 to C_{17} hydrocarbon;

R^{10} is hydrogen or C_1 to C_{17} hydrocarbon;

R^{11} is methyl or $-OR^2$; and

X and Y are independently hydrogen or halogen.

[0005] In another aspect the invention relates to methods for treating rhinitis, asthma and inflammatory diseases and conditions comprising administering the compounds of formula I.

[0006] In another aspect, the invention relates to pharmaceutical formulations for inhalation comprising the compounds of formula I, a pharmaceutically acceptable fluid for suspension or solution, and, for metered dose inhalers, additionally comprising a propellant.

Brief Description of the Drawings

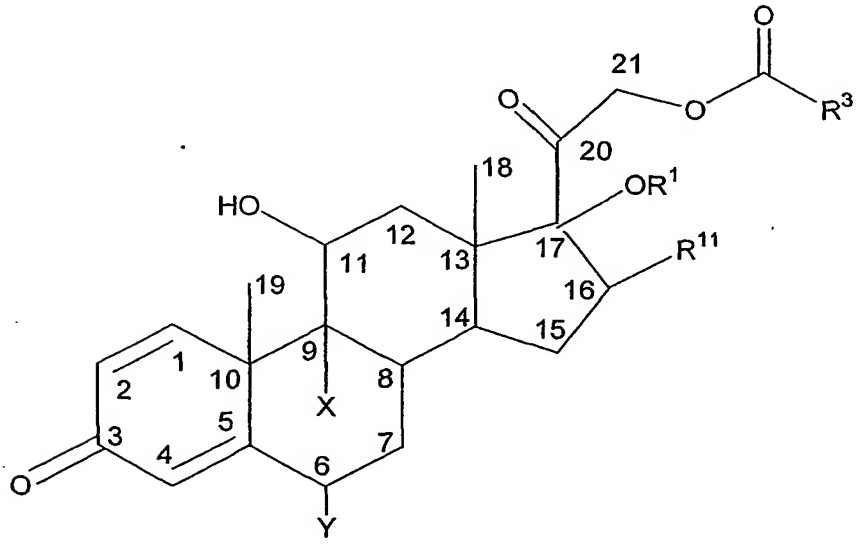
[0007] Figure 1 is a graph of the percent reduction in rat paw edema as a function of the number of carbons in a series of carbamate esters of budesonide.

[0008] Figure 2 is a graph of the percent reduction in rat paw edema as a function of the dose of budesonide at four time intervals.

[0009] Figure 3 is a graph of the percent reduction in rat paw edema as a function of the dose of budesonide dodecylcarbonate at four time intervals.

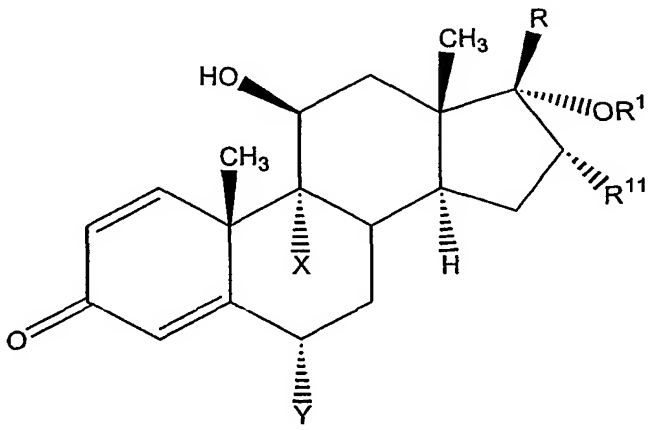
Detailed Description of the Invention

[0010] The invention relates to compounds of Formula I:

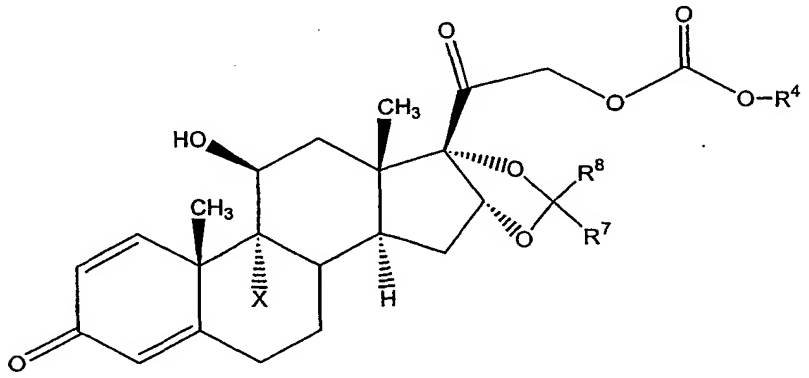


(I)

in which the substituents are as defined above. In preferred embodiments the steroid has the absolute stereochemistry shown:



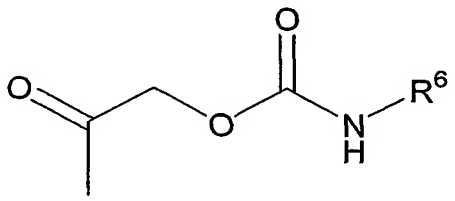
[0011] Examples of steroids having the foregoing structure include budesonide, ciclesonide, fluticasone and triamcinolone. The most preferred embodiment comprises compounds of formula:



[0012] wherein R^7 is hydrogen or lower alkyl; and R^8 is lower alkyl. In particularly preferred embodiments, R^4 is C_{11} to C_{14} alkyl, C_{12} to C_{24} alkyl, C_{12} to C_{20} alkyl, C_7 to C_{24} alkyl, C_8 to C_{24} alkyl, C_9 to C_{24} alkyl, C_{10} to C_{24} alkyl, C_{11} to C_{24} alkyl, C_8 to C_{18} alkyl, C_{10} to C_{16} alkyl or C_8 to C_{20} alkyl. In preferred embodiments the steroid is budesonide, ciclesonide or triamcinolone. Budesonide dodecyl carbonate is most preferred.

[0013] In embodiments in which R^3 is $-OR^4$ and R^4 is $-(C_7$ to C_{24} hydrocarbon)$-NR^9R^{10}$, it is preferred that the total number of carbons in R^3 be eight to twenty-four. Similarly, in embodiments in which R^3 is $-NR^5R^6$, it is preferred that the sum of the number of carbons in R^5 plus the number of carbons in R^6 be seven to twenty-four. The underlying guideline is that the total number of carbons in the residue R^3 is optimally seven to twenty-four, but an amino function could be interposed at any point that results in an R^3 residue that is chemically stable in combination with the adjacent O(C=O) residue.

[0014] In another particularly preferred embodiment, R^3 is



and R^6 is C_{11} to C_{14} alkyl, C_{12} to C_{24} alkyl, C_{12} to C_{20} alkyl, C_7 to C_{24} alkyl, C_8 to C_{24} alkyl, C_9 to C_{24} alkyl, C_{10} to C_{24} alkyl, C_{11} to C_{24} alkyl, C_8 to C_{18} alkyl, C_{10} to C_{16} alkyl or C_8 to C_{20} alkyl.

[0015] Alkyl is intended to include linear, branched, or cyclic hydrocarbon structures and combinations thereof. Preferred alkyl groups are those of C_7 to C_{24}. Cycloalkyl is a subset of alkyl and includes cyclic hydrocarbon groups, in this case preferably from 6 to 8 carbon atoms. Lower acyl is acyl of one to six carbons, e.g. acetyl, propionyl, isopropanoyl, butanoyl, sec-butanoyl, valeroyl, and hexanoyl.

[0016] C_7 to C_{24} Hydrocarbon includes alkyl, cycloalkyl, alkenyl, alkynyl, aryl and combinations thereof. Examples include phenethyl, cyclohexylmethyl, camphoryl and naphthylethyl.

[0017] The compounds described herein contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present invention is meant to include all such possible isomers, as well as, their racemic and optically pure forms. Optically active isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included. The graphic representations of racemic, ambiscalemic and scalemic or enantiomerically pure compounds used herein are taken from Maehr J. Chem. Ed. 62, 114-120 (1985): solid and broken wedges are used to denote the absolute configuration of a chiral element; wavy lines indicate disavowal of any stereochemical implication which the bond it represents could generate; solid and broken bold lines are geometric descriptors indicating the relative configuration shown but denoting racemic character; and wedge outlines and dotted or broken lines denote enantiomerically pure compounds of indeterminate absolute configuration.

[0018] The abbreviations Me, Et, Ph, Tf, Ts and Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, toluensulfonyl and methanesulfonyl respectively. A comprehensive list of abbreviations utilized by organic chemists (i.e. persons of ordinary skill in the art) appears in the first issue of each volume of the Journal of Organic Chemistry. The list, which is typically presented in a table entitled "Standard List of Abbreviations", provides the basis for the abbreviations not otherwise defined herein.

[0019] The term "methods of treating" when used in connection with the present invention means amelioration, prevention or relief from the symptoms and/or effects associated with asthma and rhinitis. The person of ordinary skill in the medical art recognizes that "prevention" of the symptoms and/or effects

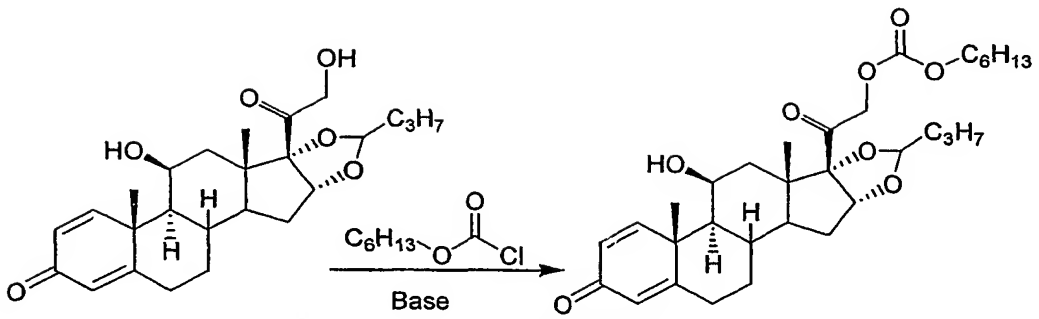
associated with asthma and rhinitis is not an absolute term. In the medical art it is understood to refer to the prophylactic administration of a drug to substantially diminish the likelihood or seriousness of the condition.

[0020] The compounds of the invention are useful for treating asthma and rhinitis. They are also useful for intra-articular injection for alleviating the joint pain, swelling and stiffness associated with rheumatoid arthritis and osteoarthritis with an inflammatory component; also for bursitis, epicondylitis and tenosynovitis. They may be used topically, transdermally and intradermally (intra-lesional) in lichen simplex chronicus, granuloma annulare, lichen planus, keloids, alopecia areata, discoid lupus erythematosus, localised neurodermatitis, cystic acne, granuloma annulare, nummular and dyshydrotic eczema, and hypertrophic scars (keloids). The treatment of macular degeneration with compounds of the invention is analogous to that described in Billson, US patent 5,770,589, which is incorporated herein by reference.

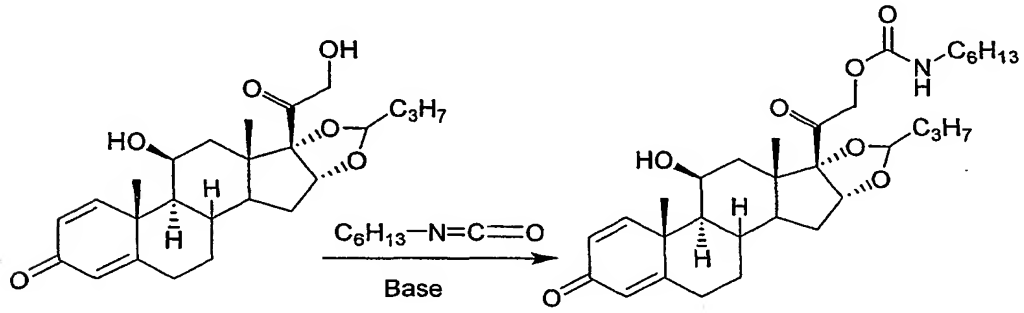
[0021] In general, the compounds of the present invention may be prepared by the methods illustrated in the general reaction schemes as, for example, described below, or by modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants that are in themselves known, but are not mentioned here.

[0022] Exemplary syntheses of a budesonide carbonate and a carbamate are shown in Schemes 1 and 2. One skilled in the art will recognize that the syntheses can be adapted to prepare a variety of carbonate or carbamate modified budesonide, ciclesonide, fluticasone or triamcinolone analogs.

Scheme 1.



Scheme 2



Synthesis of budesonide Dodecylcarbonate. (Example 2)

[0023] To the solution of budesonide (750 mg, 1.74 mmol) in DCM (7.5 mL) was added dodecyl chloroformate (513 mL, 1.617 mmol) and Et_3N (533 μL , 3.825 mmol) at room temperature. The reaction mixture was stirred at room temperature for 7 hours. During this 7 hours more dodecyl chloroformate (510 μL, 1.616 mmol) and Et_3N (440 μL, 3.18 mmol) were added. The reaction was followed by HPLC. The reaction mixture was poured into water (20 mL) and DCM (10 mL); the aqueous phase was extracted with DCM (10 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in *vacuo* to provide crude budesonide dodecylcarbonate. The product was purified by chromatography, eluted with Hexane: AcOEt = 9:1 to 3:1 to provide 983 mg of 1:1 mixture of epimers (originated from budesonide) (96.78 area % purity on HPLC). ^1H NMR ($CDCl_3$) δ 0.80-2.25 (m, 45H), 2.36 (d, 1H, 13.4Hz), 2.58 (t, 1H,

13.2Hz), 4.19 (t, 2H, 6.7 Hz), 4.52 (bs, 1H), 4.6-5.2 (m, 5H), 6.03 (s, 1H), 6.30 (d, 1H, 10.1 Hz), 7.29 (d, 1H, 10.1 Hz). ^{13}C NMR ($CDCl_3$) δ 14.21, 14.38, 17.22, 17.35, 17.50, 17.78, 21.35, 22.94, 25.86, 28.83, 29.45, 29.60, 29.74, 29.80, 29.88, 30.57, 31.24, 32.16, 33.18, 33.68, 34.26, 35.26, 37.36, 41.17, 41.41, 44.24, 46.18, 47.61, 50.01, 53.14, 55.41, 55.52, 69.12, 69.18, 70.11, 70.22, 82.32, 83.57, 97.76, 98.62, 104.88, 108.63, 122.83, 128.24, 156.14, 169.81. 169.92, 186.74, 202.16 and 203.46. Mass spectrum (m/e) 643 (M^+).

Synthesis of budesonide hexadecylcarbonate. (Example 7)

[0024] To the solution of budesonide (431 mg, 1.0 mmol) in DCM (4.5 mL) was added heaxdecyl chloroformate (655 μL, 2.0 mmol) and Et_3N (512 μL, 3.7 mmol) at room temperature. After reaction mixture was stirred at room temperature over night, it was poured into water (20 mL) and DCM (10mL); the aqueous phase was extracted with DCM (10mL). The combined organic phases were washed with water (10mL) and brine (10mL), dried over Na_2SO_4, filtered, and concentrated in *vacuo* to provide crude budesonide hexadecylcarbonate. The product was purified by chromatography, eluted with Hexane: AcOEt = 9:1 to 3:1 to provide 432 mg of 1:1 mixture of epimers (originated from budesonide) (99.38 area % purity on HPLC). ^1H NMR ($CDCl_3$) δ 0.80-2.40 (m, 53H), 2.56 (dt, 1H, 13.1 and 4.6 Hz), 4.30 (t, 2H, 6.7 Hz), 4.5-5.2 (m, 7H), 6.00 (s, 1H), 6.26 (d, 1H, 10.1 Hz), 7.3 (d, 1H, 10.1 Hz). ^{13}C NMR ($CDCl_3$) δ 14.16, 14.18, 14.34, 17.10, 17.27, 17.39, 17.71, 21.21, 22.88, 25.81, 28.79, 29.41, 29.56, 29.70, 29.76, 29.87, 30.54, 31.19, 32.11, 33.08, 33.59, 34.23, 35.19, 37.28, 40.68, 40.98, 44.37, 46.08, 47.52, 50.00, 53.07, 55.39, 55.49, 68.98, 69.73, 69.83, 69.95, 70.04, 82.10, 83.38, 97.71, 98.58, 104.70, 108.51, 122.57, 127.91, 155.08, 156.85, 170.48, 170.59, 186.84, 186.88, 202.10 and 203.38. Mass spectrum (m/e) 699 (M^+).

Synthesis of budesonide decylcarbonate. (Example 8)

[0025] To the solution of budesonide (431 mg, 1.0 mmol) in DCM (4.5 mL) was added decyl chloroformate (460 μL, 2.0 mmol) and Et_3N (512 μL, 3.7

mmol) at room temperature. After the reaction mixture was stirred at room temperature over night, it was poured into water (20 mL) and DCM (10mL); the aqueous phase was extracted with DCM (10mL). The combined organic phases were washed with water (10mL) and brine (10mL), dried over Na_2SO_4, filtered, and concentrated in *vacuo* to provide crude budesonide decylcarbonate. The product was purified by chromatography, eluted with Hexane: AcOEt = 9:1 to 3:1 to provide 348 mg of 1:1 mixture of epimers (originated from budesonide) (99.22 area % purity on HPLC). ^{1}H NMR ($CDCl_3$) δ 0.85-2.24 (m, 42H), 2.36 (dd, 1H, 13.4 and 2.9 Hz), 2.59 (dt, 1H, 13.5 and 4.5 Hz), 4.18 (t, 1H, 6.7 Hz), 4.51 (s, 1H), 4.6-5.2 (m, 5H), 6.03 (s, 1H), 6.30 (d, 1H, 10.1 Hz), 7.49 (d, 1H, 10.1 Hz). ^{13}C NMR ($CDCl_3$) δ 14.14, 14.17, 14.31, 17.06, 17.24, 17.36, 17.68, 21.19, 22.83, 25.78, 28.76, 29.37, 29.40, 29.66, 30.52, 31.16, 32.04, 33.05, 33.56, 34.22, 35.16, 37.25, 40.58, 40.89, 44.38, 46.06, 47.49, 49.98, 53.05, 55.38, 55.48, 68.90, 68.94, 69.65, 69.75, 69.92, 70.01, 82.05, 83.34, 97.69, 98.56, 104.65, 108.47, 122.51, 127.84, 155.04, 156.96, 170.61, 170.71, 186.84, 186.89, 202.08 and 203.37. Mass spectrum (m/e) 615 (M^+).

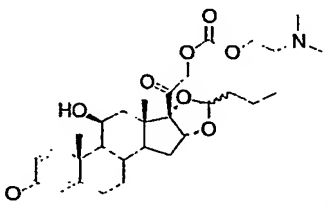
Synthesis of budesonide butylcarbamate. (Example 6)

[0026] To the solution of budesonide (500 mg, 1.16 mmol) in DCM (5.0 mL) was added butyl isocyanate (144 μL, 1.28 mmol) and DMAP (312 mg, 2.55 mmol) at room temperature. The reaction mixture was stirred at room temperature for 24 hours. During this 24 hours more butyl isocyanate (72 μL, 0.64 mmol) and DMAP (156 mg, 1.27 mmol). The reaction was followed by HPLC. The reaction mixture was poured into water (20 mL) and DCM (10 mL); the aqueous phase was extracted with DCM (10 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in *vacuo* to provide crude budesonide butylcarbamate. The product was purified by chromatography, eluted with Hexane: AcOEt = 9:1 to 3:1 to provide 560 mg of 1:1 mixture of epimers (originated from budesonide) (99.22 area % purity on HPLC). ^{1}H NMR

($CDCl_3$) δ 0.82-2.7 (m, 30H), 3.06-3.20 (m, 3H), 4.45 (m, 1H), 4.58 (t, 1H, 4.5 Hz), 4.75-5.36 (m, 5H), 5.99 (s, 1H), 6.24 (d, 1H, 10.1 Hz), 7.29 (d, 1H, 10.1Hz). ^{13}C NMR ($CDCl_3$) δ 13.98, 14.08, 14.22, 17.09, 17.30, 17.37, 17.73, 20.09, 20.28, 21.26, 30.56, 31.22, 32.11, 32.59, 33.13, 33.65, 34.27, 35.23, 37.34, 40.30, 40.73, 40.99, 41.17, 44.37, 46.09, 47.49, 50.01, 53.15, 55.43, 55.52, 67.82, 69.82, 69.93, 82.11, 83.37, 97.84, 98.75, 104.66, 108.43, 122.61, 127.97, 155.94, 156.03, 156.79, 170.45, 170.56, 186.95, 203.89 and 205.21.

Synthesis of budesonide 2-dimethylaminoethyl carbonate. (Example 20)

[0027] To the solution of budesonide (600 mg, 1.394 mmol) in DCM (5.0 mL) was added CDI (249 mg, 1.53 mmol) at RT. After 3 hr stirring, N, N-dimethylethanolamine (308 μL, 3.07 mmol) was added at room temperature. After the reaction mixture was stirred at room temperature for 3.5 hours, it was poured into water (20 mL) and DCM (10 mL); the aqueous phase was extracted with DCM (10 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in *vacuo* to provide crude budesonide 2-dimethylaminoethyl carbonate. The product was purified by chromatography, eluted with AcOEt, then AcOEt: MeOH = 98:2 to 95:5 to provide 307 mg of 1:1 mixture of epimers (originated from budesonide) (98.49 area % purity on HPLC). ^1H NMR ($CDCl_3$) δ 0.80-2.55 (m, 29H), 3.69 (bs, 1H), 4.17 (t, 2H, 5.8 Hz), 4.42 (bs, 1H), 4.4-4.95 (m, 3H), 5.05 (dd, 1H, 12.5 and 7.2 Hz), 5.92 (s, 1H), 6.28 (d, 1H, 10.1 Hz), 7.29 (d, 1H, 10.1 Hz). ^{13}C NMR ($CDCl_3$) δ 14.16, 14.21, 17.08, 17.20, 17.37, 17.69, 21.22, 30.52, 31.18, 32.10, 33.06, 33.60, 34.28, 35.16, 37.24, 40.65, 40.94, 44.46, 45.86, 46.23, 47.64, 49.99, 53.11, 55.36, 55.45, 57.56, 66.27, 66.30, 69.34, 69.45, 70.14, 70.18, 82.14, 83.41, 97.76, 98.62, 104.64, 108.42, 122.48, 127.73, 154.92, 157.26, 157.37, 170.75, 170.89, 187.00, 187.08, 201.97 and 203.29.



(5)

The following compounds were synthesized as described above:

Example	Name	mol. Wt.
1	Budesonide isobutylcarbonate	530.65
2	Budesonide dodecylcarbonate	642.87
3	Budesonide hexylcarbonate	558.71
4	Budesonide dibutylcarbamate	585.77
5	Dexamethasone dodecylcarbonate	604.8
6	Budesonide butylcarbamate	529.67
7	Budesonide hexadecylcarbonate	698.98
8	Budesonide decylcarbonate	614.81
9	Budesonide hexylcarbonate	558.71
10	Budesonide dodecylcarbonate	642.86
11	Budesonide nonylcarbonate	600.78
12	Budesonide octycarbonate	586.76
13	Budesonide undecylcarbamate	627.85
14	Budesonide heptylcarbonate	572.73
15	Budesonide 11-dimethylaminoundecylcarbonate	671.9
16	Budesonide phytolcarbonate	753.07
17	Budesonide farnesolcarbonate	678.90
18	Budesonide geraniolcarbonate	610.78
19	Budesonide nerolcarbonate	610.78

[0028] For administration, the drug is suitably inhaled from a nebulizer, from a pressurized metered dose inhaler or as a dry powder from a dry powder inhaler (e.g. sold as TURBUHALER®) or from a dry powder inhaler utilizing gelatin, plastic or other capsules, cartridges or blister packs.

[0029] A diluent or carrier, generally non-toxic and chemically inert to the medicament, e.g. lactose, dextran, mannitol or glucose or any additives that will give the medicament a desired taste, can be added to the powdered medicament.

[0030] Formulations and devices for nebulizers, metered dose inhalers and dry powder inhalers are well known to those skilled in the art. In formulations where the active ingredient is in a suspension it is important that the particles are below 20 μm in size and preferably below 5 μm in size. This may be achieved by micronization, crystallization, spray drying or other known techniques.

[0031] The solvent or suspension agent utilized for nebulization may be any pharmacologically suitable fluid such as water, aqueous saline, alcohols or glycols, e.g., ethanol, isopropylalcohol, glycerol, propylene glycol, polyethylene glycol, etc. or mixtures thereof. Saline solutions utilize salts which display little or no pharmacological activity after administration. Both inorganic salts, such as alkali metal or ammonium halogen salts e.g. sodium chloride, potassium chloride or organic salts, such as potassium, sodium and ammonium salts of organic acids, e.g., ascorbic acid, citric acid, acetic acid, tartaric acid, etc. may be used for this purpose.

[0032] Other excipients and additives may be added to the formulation. The active ingredient may be stabilized by the addition of an inorganic acid, e.g., hydrochloric acid, nitric acid, sulphuric acid and/or phosphoric acid; an organic acid, e.g., ascorbic acid, citric acid, acetic acid, and tartaric acid etc.; a complexing agent such as EDTA or citric acid and salts thereof; or an antioxidant such as vitamin E or ascorbic acid. These may be used alone or together to stabilize the active ingredient. Preservatives can also be added such as benzalkonium chloride or benzoic acid and salts thereof. Surfactant may be added particularly to improve the physical stability of suspensions. These include lecithins, disodium dioctylsulphosuccinate, oleic acid and sorbitan esters.

[0033] The active ingredient may also be suspended or dissolved in a liquified propellant, sealed in a container with a metering valve and fitted into an actuator. Such metered dose inhalers are well known in the art. The metering valve may meter 10 to 500 μL and preferably 25 to 150 μL.

[0034] The propellants used may be halocarbons, hydrocarbons or other liquified gasses. The most frequently used are trichlorofluoromethane (propellant 11), dichlorfluoromethane (propellant 12), dichlortetrafluoroethane (propellant 114), tetrafluoroethane (HFA-134a), 1,1-difluoroethane (HFA-152a), difluoromethane (HFA-32), pentafluoroethane (HFA-125),

heptafluoropropane (HFA-227ea), perfluoropropane, perfluorobutane, perfluorpentane, butane, isobutane, and pentane. In particular, tetrafluoroethane (HFA-134a) and heptafluoropropane (HFA-227ea) and mixtures thereof are used.

[0035] As well as propellant, formulations may contain other excipients. Surfactant may be added particularly to improve the physical stability of suspensions and valve performance. These include lecithins, disodium dioctylsulphosuccinate, oleic acid and sorbitan esters. Cosolvents may also be added to improve solubility of surfactant in propellant or modify the pharmacological performance. These include alcohols and glycols, e.g., ethanol, isopropylalcohol, glycerol, propylene glycol, polyethylene glycol, etc., or mixtures thereof. Further excipients may be added to improve performance or taste, e.g., fatty acids and salts thereof such as magnesium stearate, menthol oil etc.

[0036] Dry powder inhalers include devices which meter drug from a chamber within the device or those that deliver pre-metered doses utilizing gelatin, plastic or other capsules, cartridges, or blister packs and/or strips.

[0037] For topical application, there are employed as non-sprayable forms, viscous to semi-solid or solid forms comprising a carrier compatible with topical application and having a dynamic viscosity preferably greater than water. Suitable formulations include but are not limited to solutions, suspensions, emulsions, creams, ointments, powders, liniments, salves, aerosols, etc., which are, if desired, sterilized or mixed with auxiliary agents, e.g., preservatives, stabilizers, wetting agents, buffers or salts for influencing osmotic pressure, etc. For topical application, also suitable are sprayable aerosol preparations wherein the active ingredient, preferably in combination with a solid or liquid inert carrier material, is packaged in a squeeze bottle or in admixture with a pressurized volatile, normally gaseous propellant, e.g., a freon.

[0038] The topical pharmaceutical carrier may include any substance capable of dispersing and maintaining contact between the active ingredients and the skin. The vehicle may be glycerin, alcohol or water based. Examples of such vehicles include aloe vera, which is a gel base, together with ethanol, isopropyl alcohol, water, propylene glycol and a non-ionic surfactant such as laureth-4. Other water-based alcohol/ glycerin vehicles and carriers are within the scope of the present invention. A typical water-based lotion will contain from 45 to 50 parts of glycerin, one to three parts Tween 80TM, from 45 to 50 parts of water and from 1 to 50 parts of the compound of the invention.

[0039] Also included in the scope of the invention are ointments, emulsions or dispersions in which water, if present, is a minor constituent. Typical ointment formulation comprises from 90 to 98 parts of a mixture of petrolatum, mineral oil, mineral wax and wool wax alcohol, from 0.5 to 3 parts of a mixture of polyoxyethylene and sorbitan monooleate (Tween 80TM), from 1 to 5 parts of water, and from 1 to 50 parts of the compound of the invention. Another suitable non-aqueous ointment can be prepared from 95 parts of liquid petrolatum USP, 5 parts polyethylene and from 1 to 50 parts of the compound of the invention. The resulting ointment spreads easily and has an even consistency over wide temperature extremes. It is, in addition, non-irritating and non-sensitizing.

[0040] Formulations of the compounds of the invention may also be prepared containing from 0 to 25% by weight of urea. In general, in such urea containing ointments, the water content will vary from 5 to 50% by weight of the composition. Any suitable ointment carrier may be used such as lanolin, ethylene glycol polymers and the like. In the case of formulations containing urea, it is known in the art that borate salts may often be added to stabilize the pharmaceutical composition (see U.S. patent 2,917,433, the disclosure of which is incorporated herein by reference).

[0041] Water based compositions may also be employed, in which case the compound of the invention will commonly be in solution, and the aqueous solution may, if desired, be thickened with a suitable gel to provide a less mobile composition. Such compositions are well known in the art

[0042] Compounds as described above were tested in the following assay for biological activity. The WI-38 human lung fibroblast line was obtained from the ATCC (catalog number 75-CCL) and maintained in Basal Medium Eagle with Earle's salts (GibcoBRL product number 21010-046) supplemented with 2 mM glutamine and 10% fetal calf serum at 37°C in a 7% CO_2 (balance air), humidified atmosphere. One week before experiments were done, the WI-38 cells were seeded into 48-well tissue culture dishes and maintained in media containing 10% fetal calf serum. The cells were used when confluent. The day before the experiment the cells were fed fresh media containing 10% fetal calf serum (0.25 mL per well). One the day of the experiment the media was removed from the cells and 0.25 mL of media containing 5% fetal calf serum added.

[0043] The rat alveolar macrophage cell line RAW 264.7 was obtained from the ATCC (catalog number 71-TIB) and maintained in Dulbecco's Modified Eagle Medium (GibcoBRL product number 11960-044) supplemented with 2 mM glutamine, 1 mM sodium pyruvate and 10% fetal calf serum at 37°C in a 10% CO_2 (balance air), humidified atmosphere. One week before experiments were done, the WI-38 cells were seeded into 48-well tissue culture dishes and maintained in media containing 10% fetal calf serum. The cells were used when confluent. The day before the experiment the cells were fed fresh media containing 10% fetal calf serum (0.25 mL per well). One the day of the experiment the media was removed from the cells and 0.25 mL of media containing 5% fetal calf serum added.

[0044] To determine the IC_{50} values for the compounds, 1 to 1000 dilutions were made of the 5 mM stock solutions in DMSO to give 5 uM solutions.

These solutions were serially diluted 1:2 in DMSO to give a series of 12 dilutions ranging from 5 uM to 2.4 nM. 0.0025 mL aliquots of the 12 dilutions were added to wells of the WI-38 cells to give final compound concentrations ranging from 50 nM to 0.024 nM. The cells were stimulated by addition of 0.001 mL of 0.025 ug/mL recombinant human Interleukin-1β (IL-1β - Calbiochem catalog number 407615) in 0.1% bovine serum albumin in phosphate buffered saline. The cells were incubated for 24 hours and the supernatants harvested. The level of PGE_2 in the supernatants was assayed using a commercial Enzyme Immuno Assay (EIA) kit (Cayman Chemical catalog number 514010) after diluting 1:10 in EIA buffer according to the manufacturer's directions. The data from these experiments was fit to a 4 parameter logistic function using the IC_{50} routine in the Grafit 4 program (Erithecus software). IC_{50} values determined in this manner were: budesonide 0.20 nM; budesonide isobutylcarbonate 0.12 nM; budesonide dodecylcarbonate 0.53 nM; budesonide hexylcarbonate 0.14 nM.

[0045] The compounds of the invention were also tested *in vivo* in a rat paw edema model [Hirschelmann, R. and Bekemeier, H., Int J Tissue React 6, 471-475 (1984)], which persons of skill in the art accept as predictive of efficacy in treating asthma and rhinitis in humans.

[0046] Rat Paw Edema Protocol: Male Sprague Dawley rats Rj: SD (IOPS Han) (CEJ, France) weighing between 140 and 160 grams were used in the studies. Animals were housed in a temperature (19.5 – 24.5 °C), relative humidity (40 – 70%) and 12-hour light/dark cycle (light 6:00 a.m. to 6:00 p.m.)-controlled room, with *ad libitum* access to filtered tap-water and standard pelleted laboratory chow (U.A.R., France) throughout the studies. Carrageenan lambda type IV (Sigma, France) was prepared as a 2% (w/v) solution in saline. Compounds to be tested were dissolved in dimethylsulfoxide (DMSO) such that the indicated doses were in a final volume of 0.05 mL. Doses were expressed as mg/paw free active substance. From 17 to 19 hours before the studies the rats were fasted with free access to water. The paw volumes of the

left hindpaws of the rats were measured using an electronic plethysmometer type 7140 (Ugo Basile – Italy) at time = 0. Paw edema was then induced by injection of 0.05 mL of 2% carrageenan solution into the left hindpaws of the rats. Immediately after injection of the carrageenan, compounds in DMSO or vehicle alone were injected into the same paw in a volume of 0.05 mL in a blind and random fashion.

[0047] The paw volumes were measured at 1.5 hours, 3 hours, 4.5 hours and 24 hours after administration of the compounds. The edema volume of each rat at each time point was expressed as the change from the initial paw volume (time = 0). A total of 5 rats were used for each compound dose and the average edema volume calculated for each dose. The anti-inflammatory effect in treated groups was expressed as the percent inhibition of edema volume compared to the vehicle-treated group at 1.5 hours, 3 hours, 4.5 hours and 24 hours.

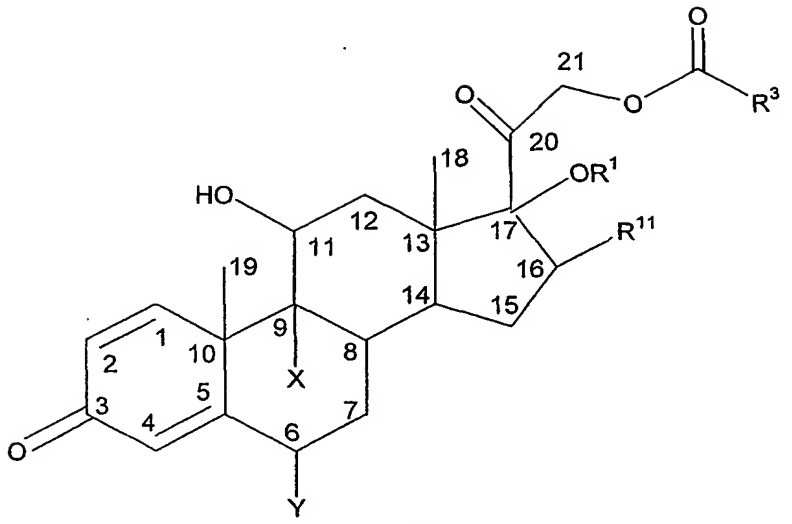
[0048] The results are shown in Figure 1, in which the efficacies of equimolar doses (equivalent to 10 μg per paw of budesonide) are compared at 24 hours. Budesonide itself reduces swelling by 46%. The formation of a carbonate ester at C21 decreases the efficacy of budesonide when the ester is C_6 or smaller. Unexpectedly, at C_6 the curve reverses, and the efficacy increases. Thus, although one would expect C_7 to be less efficacious than C_6, in fact it is surprisingly found more efficacious, and the C_{10} carbonate is 30% more efficacious than budesonide itself. The correlation between numbers of carbons in the carbonate ester and efficacy reaches a peak at C_{12} with an 88% reduction of swelling.

[0049] Other carbonates showed similar behavior. The phytol (Example 16) and farnesol (Example 17) carbonates exhibited normal onset of action and maximum activity at 24 hours of 69 and 86 percent respectively. The amine-terminal alkylcarbonate, Example 15, exhibited a maximum activity at 24 hours of 73 percent.

[0050] The enhanced effect of the carbonates and carbamates compared to the parent steroid is most dramatic at the 24-hour observation, as can be seen by comparing Figures 2 and 3, in which budesonide carbonate is compared to budesonide.

CLAIMS

1. A compound of Formula I:



(I)

wherein

R^1 and R^2, independently for each occurrence, represent a hydrogen, lower alkyl or lower acyl, or taken together R^1 and R^2 form a substituted or unsubstituted ketal;

R^3 is $-OR^4$ or $-NR^5R^6$;

R^4 is chosen from C_7 to C_{24} hydrocarbon, -(C_7 to C_{24} hydrocarbon)-COOH and -(C_7 to C_{24} hydrocarbon)-NR^9R^{10};

R^5 is hydrogen or C_7 to C_{24} hydrocarbon;

R^6 is chosen from C_7 to C_{24} hydrocarbon and -(C_7 to C_{24} hydrocarbon)-COOH;

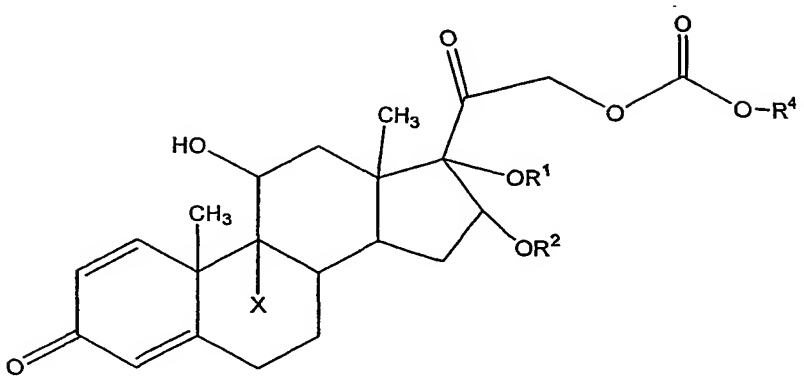
R^9 is hydrogen or C_1 to C_{17} hydrocarbon;

R^{10} is hydrogen or C_1 to C_{17} hydrocarbon;

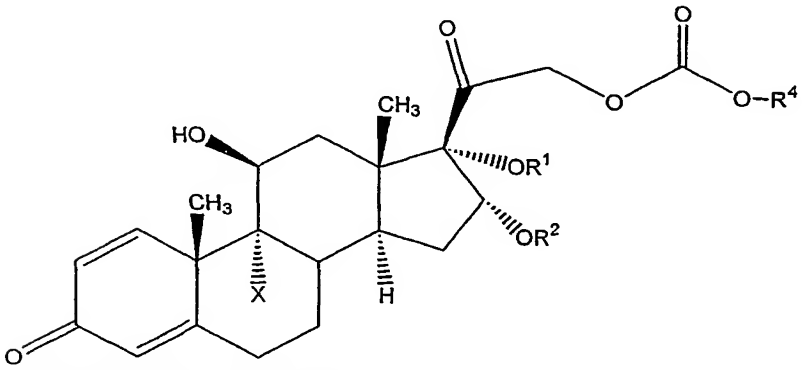
R^{11} is methyl or $-OR^2$; and

X and Y are independently hydrogen or halogen.

2. A compound according to claim 1of formula:

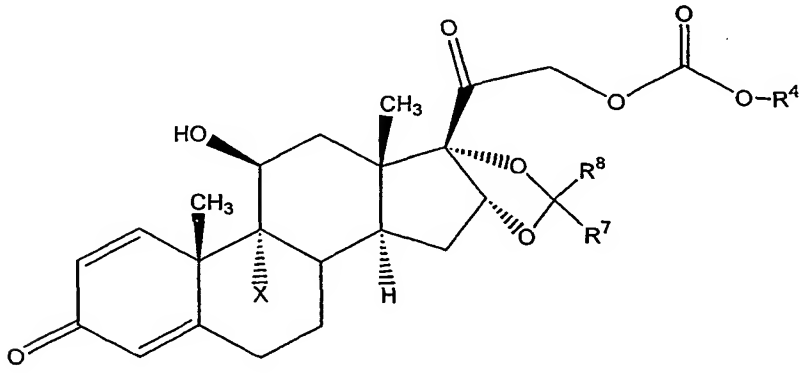


3. A compound according to claim 2 of formula:



wherein X is hydrogen or fluorine.

4. A compound according to claim 3 of formula

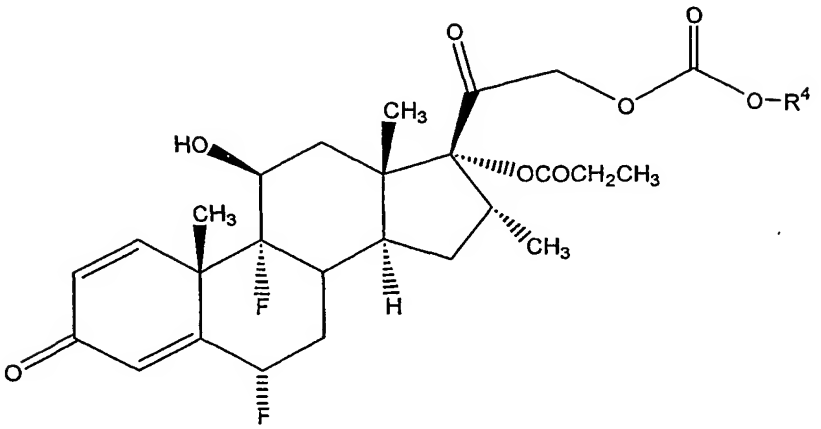


wherein

R^7 is hydrogen or lower alkyl; and

R^8 is lower alkyl.

5. A compound according to claim 1 of formula



6. A compound according to any of claims 1 to 5 wherein R^4 is C_{11} to C_{14} alkyl.

7. A compound according to any of claims 1 to 5 wherein R^4 is C_{11} to C_{18} alkyl.

8. A compound according to any of claims 1 to 5 wherein R^4 is C_{12} to C_{24} alkyl.

9. A compound according to any of claims 1 to 5 wherein R^4 is C_{12} to C_{20} alkyl.

10. A compound according to any of claims 1 to 5 wherein R^4 is C_7 to C_{24} alkyl.

11. A compound according to any of claims 1 to 5 wherein R^4 is C_8 to C_{24} alkyl.

12. A compound according to any of claims 1 to 5 wherein R^4 is C_9 to C_{24} alkyl.

13. A compound according to any of claims 1 to 5 wherein R^4 is C_{10} to C_{24} alkyl.

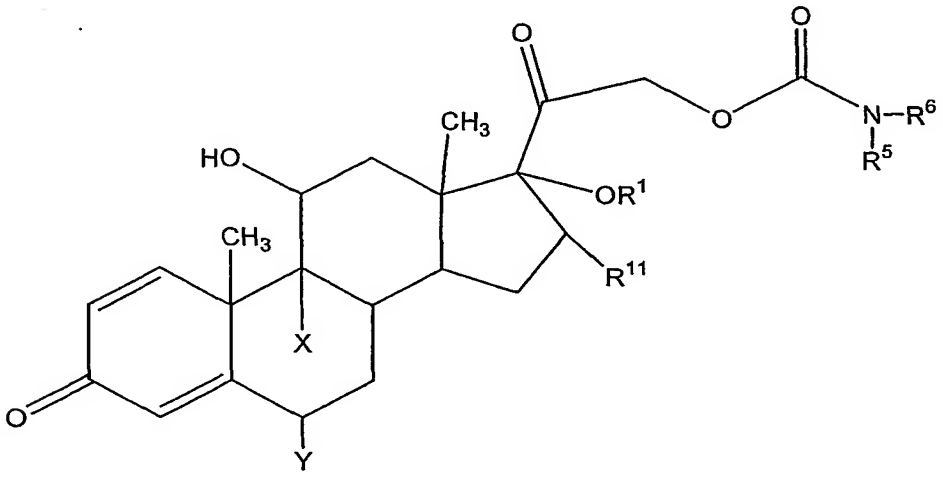
14. A compound according to any of claims 1 to 5 wherein R^4 is C_{11} to C_{24} alkyl.

15. A compound according to any of claims 1 to 5 wherein R^4 is C_8 to C_{18} alkyl.

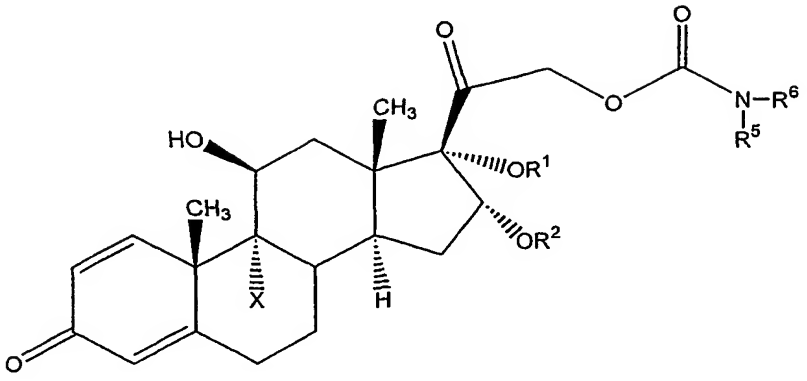
16. A compound according to any of claims 1 to 5 wherein R^4 is C_{10} to C_{16} alkyl.

17. A compound according to any of claims 1 to 5 wherein R^4 is C_8 to C_{20} alkyl.

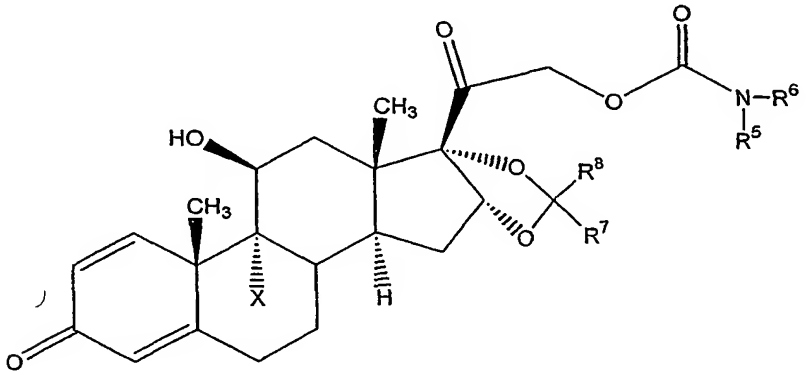
18. A compound according to claim 1of formula:



19. A compound according to claim 18 of formula:



20. A compound according to claim 19 of formula

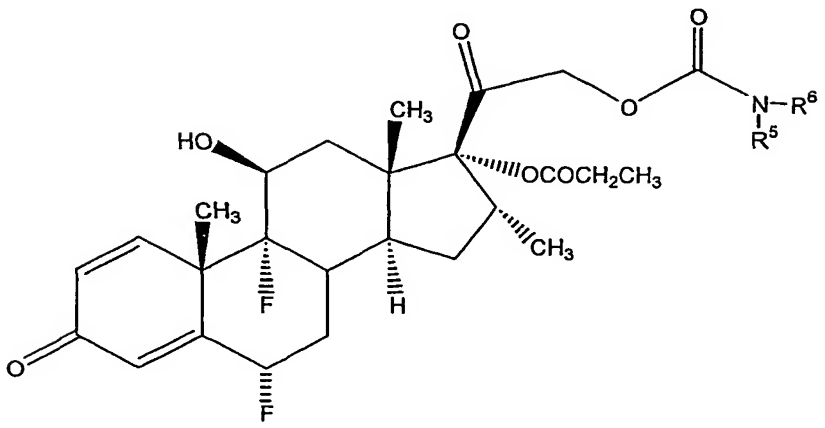


wherein

R^7 is hydrogen or lower alkyl; and

R^8 is lower alkyl.

21. A compound according to claim 18 of formula



22. A compound according to any of claims 18 to 21 wherein R^5 is hydrogen or lower alkyl.

23. A compound according to any of claims 18 to 21 wherein R^6 is C_{11} to C_{14} alkyl.

24. A compound according to any of claims 18 to 21 wherein R^6 is C_{11} to C_{18} alkyl.

25. A compound according to any of claims 18 to 21 wherein R^6 is C_{12} to C_{24} alkyl.

26. A compound according to any of claims 18 to 21 wherein R^6 is C_{12} to C_{20} alkyl.

27. A compound according to any of claims 18 to 21 wherein R^6 is C_7 to C_{24} alkyl.

28. A compound according to any of claims 18 to 21 wherein R^6 is C_8 to C_{24} alkyl.

29. A compound according to any of claims 18 to 21 wherein R^6 is C_9 to C_{24} alkyl.

30. A compound according to any of claims 18 to 21 wherein R^6 is C_{10} to C_{24} alkyl.

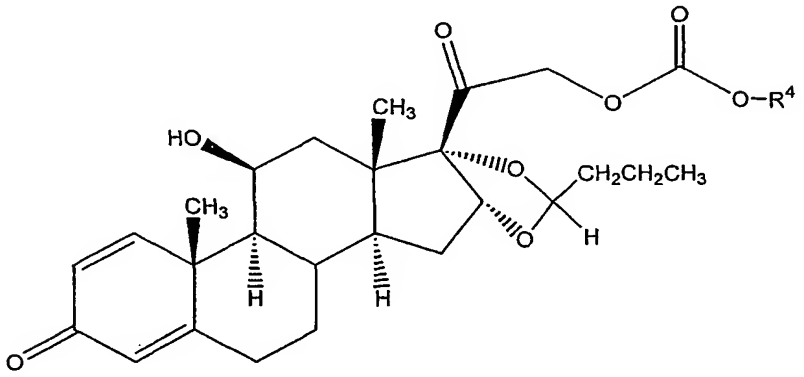
31. A compound according to any of claims 18 to 21 wherein R^6 is C_{11} to C_{24} alkyl.

32. A compound according to any of claims 18 to 21 wherein R^6 is C_8 to C_{18} alkyl.

33. A compound according to any of claims 18 to 21 wherein R^6 is C_{10} to C_{16} alkyl.

34. A compound according to any of claims 18 to 21 wherein R^6 is C_8 to C_{20} alkyl.

35. A compound according to claim 3 of formula



wherein R^4 is n-dodecyl.

36. A method for treating rhinitis comprising administering the compound of any of claims 1-35.

37. A method for treating asthma comprising administering the compound of any of claims 1-35.

38. A method according to either of claims 36 or 37 wherein said compound is administered by inhalation.

39. A method for treating a disorder chosen from osteoarthritis, bursitis, epicondylitis, tenosynovitis, lichen simplex chronicus, granuloma annulare, lichen planus, keloids, alopecia areata, discoid lupus erythematosus, localised neurodermatitis, cystic acne, granuloma annulare, nummular and dyshydrotic eczema, hypertrophic scars and macular degeneration comprising administering the compound of any of claims 1-35.

40. A pharmaceutical formulation for inhalation comprising a compound according to any of claims 1-35 and a pharmaceutically acceptable fluid for suspension or solution.

41. A pharmaceutical formulation for inhalation according to claim 40 additionally comprising a propellant.

42. A pharmaceutical formulation for topical application comprising a compound according to any of claims 1-35 and a pharmaceutically acceptable carrier for topical or transdermal application.

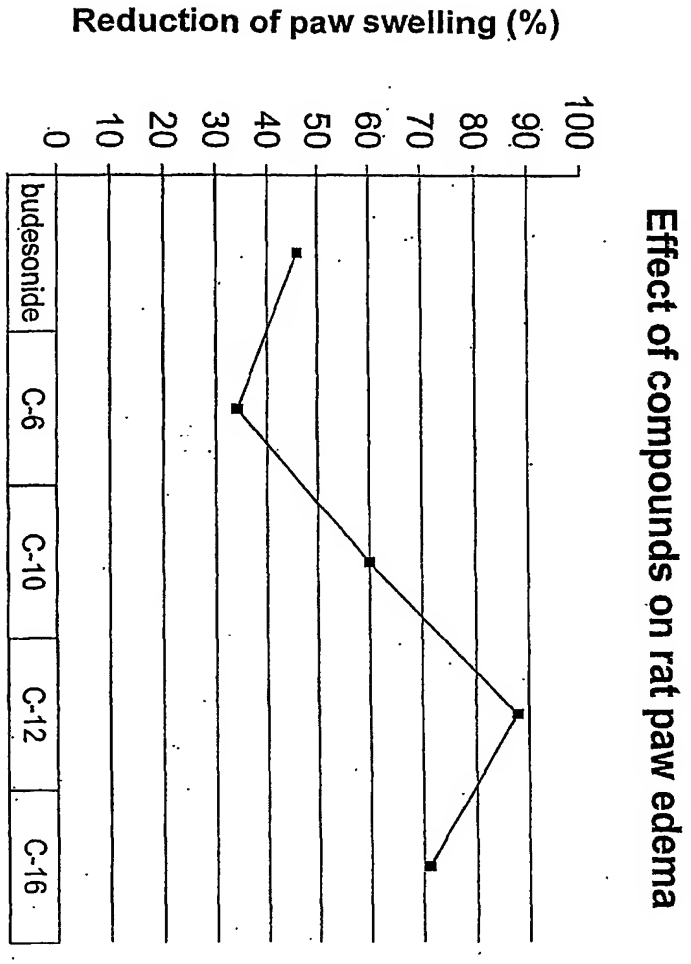


FIG. 1

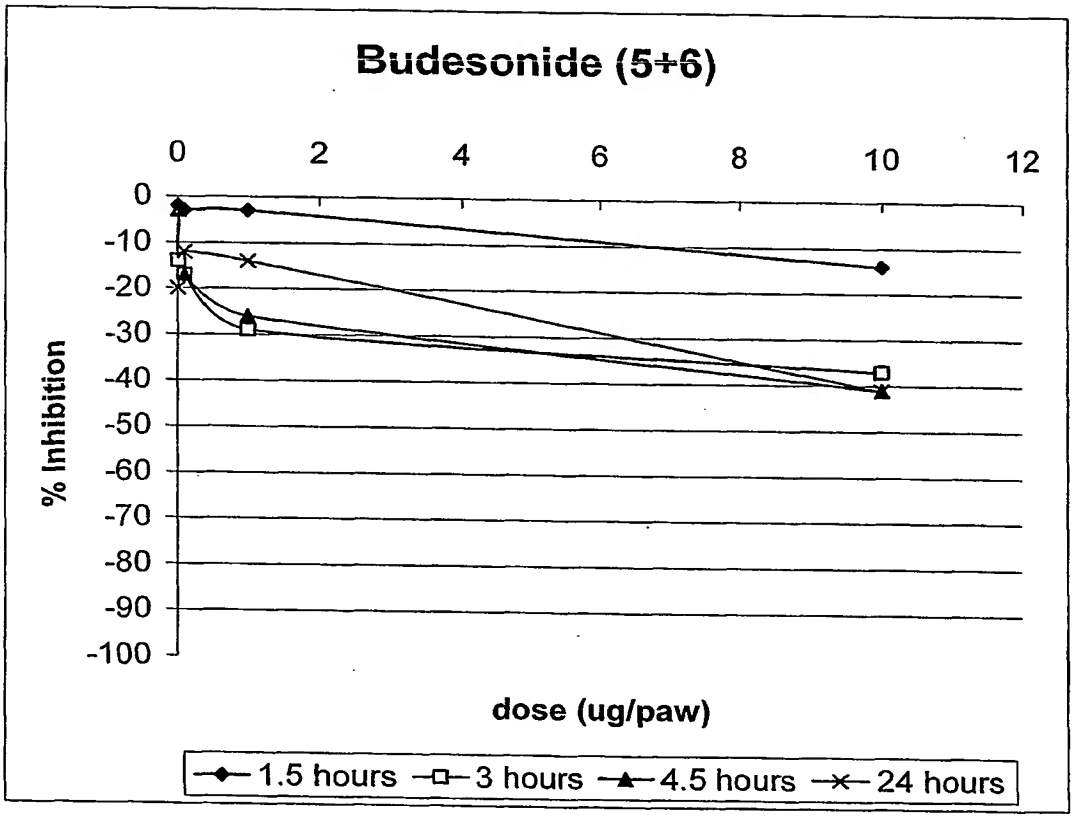

Budesonide (5+6)
0
2
4
6
8
10
12
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
% Inhibition
dose (ug/paw)
1.5 hours
3 hours
4.5 hours
24 hours

FIG. 2

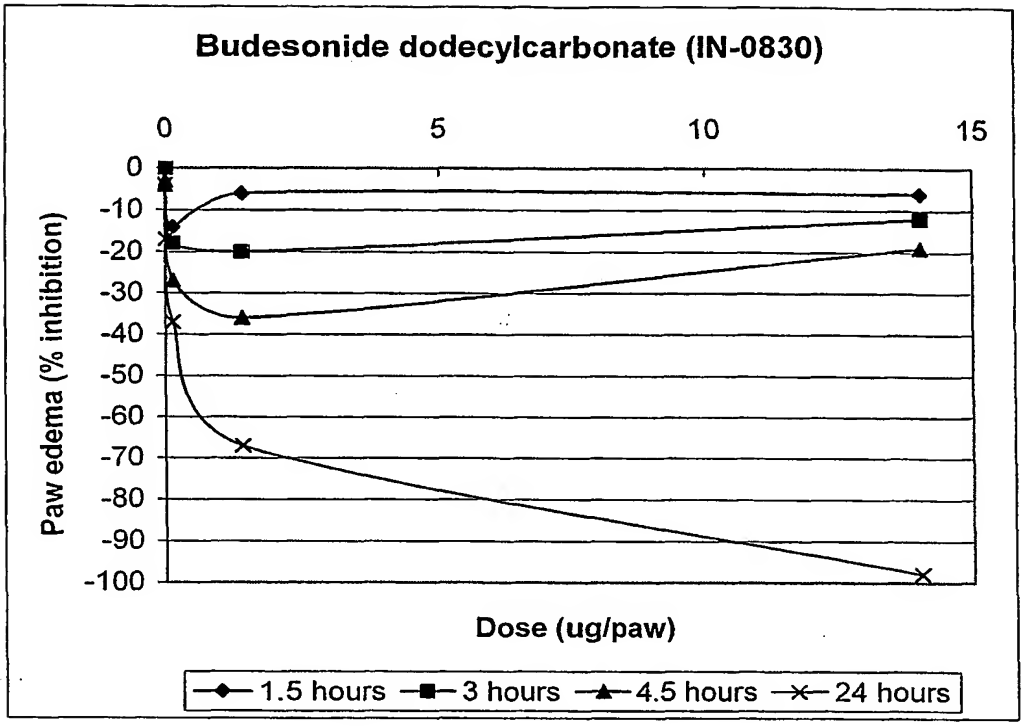

Budesonide dodecylcarbonate (IN-0830)
0
5
10
15
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
Paw edema (% inhibition)
Dose (ug/paw)
1.5 hours
3 hours
4.5 hours
24 hours

FIG. 3

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 August 2003 (28.08.2003)

PCT

(10) International Publication Number
WO 03/070745 A3

(51) International Patent Classification[7]: C07J 43/00, A61K 31/573, 31/58, A61P 5/44, C07J 41/00, 71/00, 5/00

(21) International Application Number: PCT/US03/04655

(22) International Filing Date: 18 February 2003 (18.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/358,246 20 February 2002 (20.02.2002) US
60/428,180 21 November 2002 (21.11.2002) US

(71) Applicant *(for all designated States except US)*: SEPRACOR INC. [US/US]; 84 Waterford Drive, Marlborough, MA 01752 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: GROVER, Paul [US/US]; 4 Warwick Road, Franklin, MA 02038 (US). JONES, Steve [US/US]; 10 Ragged Hill Road, Milford, MA 01757 (US). SENANAYAKE, Chris, H. [US/US]; 12 Isabel's Way, Brookfield, CT 06804 (US). CURRIE, Mark, G. [US/US]; 18 Hall Avenue, Sterling, MA 01564 (US). FANG, Q., Kevin [US/US]; 35 Atwood Street, Wellesley, MA 02181 (US).

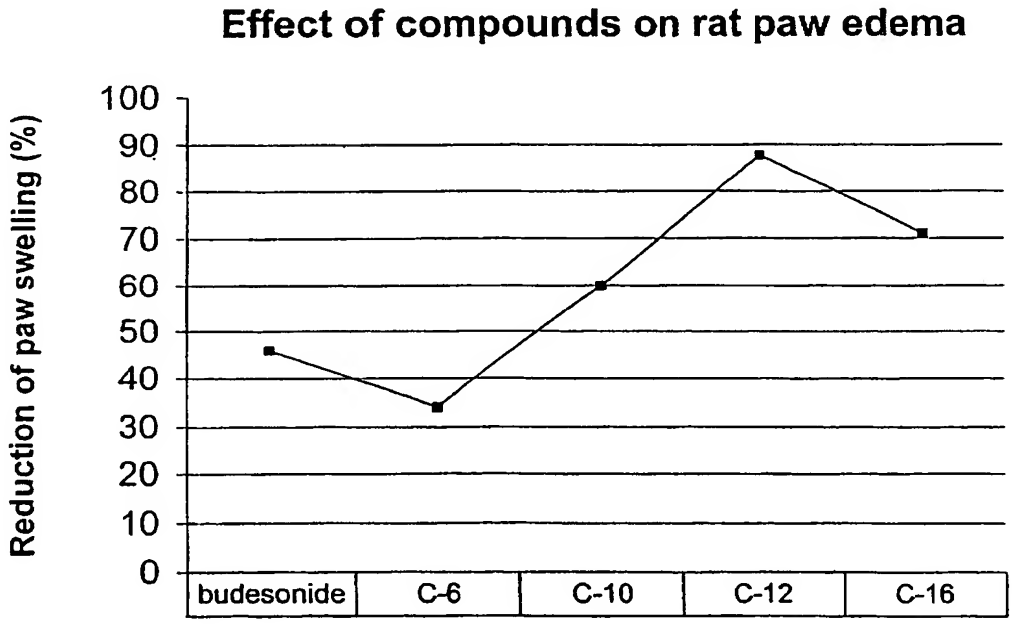
(74) Agent: HANSEN, Philip E.; HESLIN ROTHENBERG FARLEY & MESITI P.C., 5 Columbia Circle, Albany, NY 12203 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,

[Continued on next page]

(54) Title: CARBONATE AND CARBAMATE MODIFIED FORMS OF GLUCOCORTICOIDS



(57) Abstract: Carbonates and carbamates of the formula and related steroid carbonates and carbamates are disclosed. The compounds are useful for treating rhinitis and asthma, particularly by inhalation, and for treating inflammation, particularly by local or topical administration.

WO 03/070745 A3

ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
20 November 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/04655

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07J43/00 A61K31/573 A61K31/58 A61P5/44 C07J41/00
C07J71/00 C07J5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07J A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
PAJ, WPI Data, EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 329 570 A (LES LILAS ET AL) 4 July 1967 (1967-07-04) examples I,V	1,36-42
X	WO 00 11018 A (FREY BRIGITTE ;FREY FELIX (CH); RUSCONI SANDRO (CH); WEHRLI HANS U) 2 March 2000 (2000-03-02) page 28, formula 13	1,10,18, 22
A	GB 1 269 291 A (SYNTEX CORP.) 6 April 1972 (1972-04-06) page 1, line 20-27 page 4, line 40-49; example 3 example 5	1-42

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

°A° document defining the general state of the art which is not considered to be of particular relevance

°E° earlier document but published on or after the international filing date

°L° document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

°O° document referring to an oral disclosure, use, exhibition or other means

°P° document published prior to the international filing date but later than the priority date claimed

°T° later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

°X° document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

°Y° document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

°&° document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 August 2003	11/09/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Watchorn, P

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	BROWN, H. D. ET AL: "Some 21-Carbamates of hydrocortisone and related compounds" JOURNAL OF ORGANIC CHEMISTRY (1962), 27, 961-3 , XP002252411 page 961, column 2, paragraph 4 page 962, column 1; table I	1-42
A	US 3 056 727 A (ANDRE ALLAIS ET AL) 2 October 1962 (1962-10-02) column 11-20; example V	1-42
A	WO 92 13873 A (ASTRA AB) 20 August 1992 (1992-08-20) cited in the application page 2, last paragraph -page 3, paragraph 1 examples 6,7,19,27,28 page 40; table 1	1-42
A	EP 0 170 642 A (DRACO AB) 5 February 1986 (1986-02-05) cited in the application page 1, paragraphs 1,2 page 17, paragraph 2 examples 1-27	1-42
P,A	WO 02 36606 A (MATRIX THERAPEUTICS LTD ;MIEL HUGHES JEAN PIERRE (GB); RAY DAVID W) 10 May 2002 (2002-05-10) page 5, paragraph 1 figure 2A; example T	1-42

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/04655

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 36-39 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 03/04655

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3329570 A	04-07-1967	FR 1512323 A	09-02-1968
		BE 657318 A	18-06-1965
		CH 437276 A	15-06-1967
		DE 1468893 A1	27-04-1972
		DK 112235 B	25-11-1968
		FR 3244 M	
		FR 4053 M	
		GB 1068099 A	10-05-1967
		IL 22646 A	26-12-1968
		NL 122815 C	
		NL 6414703 A	21-06-1965
		SE 317971 B	01-12-1969
WO 0011018 A	02-03-2000	WO 0011019 A1	02-03-2000
		AU 755710 B2	19-12-2002
		AU 5146399 A	14-03-2000
		AU 8818398 A	14-03-2000
		CA 2338342 A1	02-03-2000
		WO 0011018 A1	02-03-2000
		EP 1105408 A1	13-06-2001
		JP 2002523422 T	30-07-2002
		NZ 509294 A	28-02-2003
GB 1269291 A	06-04-1972	CA 929933 A1	10-07-1973
		CH 536299 A	30-04-1973
		DE 2017533 A1	10-12-1970
		FR 2042348 A1	12-02-1971
		NL 7005605 A	20-10-1970
US 3056727 A	02-10-1962	NONE	
WO 9213873 A	20-08-1992	AP 365 A	21-10-1994
		AT 164589 T	15-04-1998
		AU 661472 B2	27-07-1995
		AU 1235892 A	07-09-1992
		BG 61816 B1	30-06-1998
		BG 98011 A	25-04-1994
		CA 2100453 A1	05-08-1992
		CN 1064078 A ,B	02-09-1992
		CN 1155418 A ,B	30-07-1997
		CN 1158726 A ,B	10-09-1997
		CZ 9301495 A3	16-03-1994
		DE 69224982 D1	07-05-1998
		DE 69224982 T2	30-07-1998
		DK 572451 T3	19-10-1998
		EE 3110 B1	17-08-1998
		EP 0572451 A1	08-12-1993
		ES 2114931 T3	16-06-1998
		FI 933451 A	03-08-1993
		HK 1004335 A1	20-11-1998
		HU 64972 A2	28-03-1994
		IE 920167 A1	12-08-1992
		IL 100542 A	18-02-1997
		JP 2947933 B2	13-09-1999
		JP 6505233 T	16-06-1994
		KR 205835 B1	01-07-1999
		MX 9200374 A1	01-08-1992
		NO 932762 A	02-08-1993

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 03/04655

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9213873 A		NZ	241211 A	26-08-1993
		PL	170383 B1	31-12-1996
		PT	100087 A ,B	31-05-1993
		RO	111272 B1	30-08-1996
		RU	2112775 C1	10-06-1998
		WO	9213873 A1	20-08-1992
		SI	9210064 A ,B	28-02-1995
		SK	79793 A3	09-03-1994
		US	5614514 A	25-03-1997
		US	5888995 A	30-03-1999
		ZA	9200234 A	28-10-1992
EP 0170642 A	05-02-1986	AT	60990 T	15-03-1991
		AU	582173 B2	16-03-1989
		AU	4530785 A	06-02-1986
		CA	1250830 A1	07-03-1989
		CN	85105713 A ,B	28-01-1987
		CS	254342 B2	15-01-1988
		CY	1731 A	06-05-1994
		DD	236535 A5	11-06-1986
		DD	248055 A5	29-07-1987
		DE	3581856 D1	04-04-1991
		DK	336385 A ,B,	31-01-1986
		EG	17462 A	30-03-1991
		EP	0170642 A2	05-02-1986
		ES	8704969 A1	01-07-1987
		ES	8705895 A1	01-08-1987
		FI	852932 A ,B,	31-01-1986
		HK	78293 A	13-08-1993
		HR	920587 A1	31-10-1995
		HU	39460 A2	29-09-1986
		IE	58074 B1	30-06-1993
		JP	1770233 C	30-06-1993
		JP	4059297 B	21-09-1992
		JP	61043110 A	01-03-1986
		KR	9300045 B1	06-01-1993
		LT	2257 R3	15-12-1993
		LV	5527 A3	10-03-1994
		NO	852672 A ,B,	31-01-1986
		NZ	212861 A	27-01-1989
		PH	21644 A	13-01-1988
		PL	254681 A1	18-11-1986
		PT	80884 A ,B	01-08-1985
		SG	69093 G	06-08-1993
		SI	8511238 A8	31-10-1996
		SU	1493111 A3	07-07-1989
		US	4693999 A	15-09-1987
		YU	123885 A1	29-02-1988
		ZA	8505032 A	26-03-1986
WO 0236606 A	10-05-2002	AU	1076802 A	15-05-2002
		CA	2427569 A1	10-05-2002
		EP	1335928 A1	20-08-2003
		WO	0236606 A1	10-05-2002

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 August 2003 (28.08.2003)

PCT

(10) International Publication Number
WO 2003/070745 A3

(51) International Patent Classification[7]: C07J 43/00, A61K 31/573, 31/58, A61P 5/44, C07J 41/00, 71/00, 5/00

(21) International Application Number: PCT/US2003/004655

(22) International Filing Date: 18 February 2003 (18.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/358,246 20 February 2002 (20.02.2002) US
60/428,180 21 November 2002 (21.11.2002) US

(71) Applicant (*for all designated States except US*): SEPRACOR INC. [US/US]; 84 Waterford Drive, Marlborough, MA 01752 (US).

(72) Inventors; and

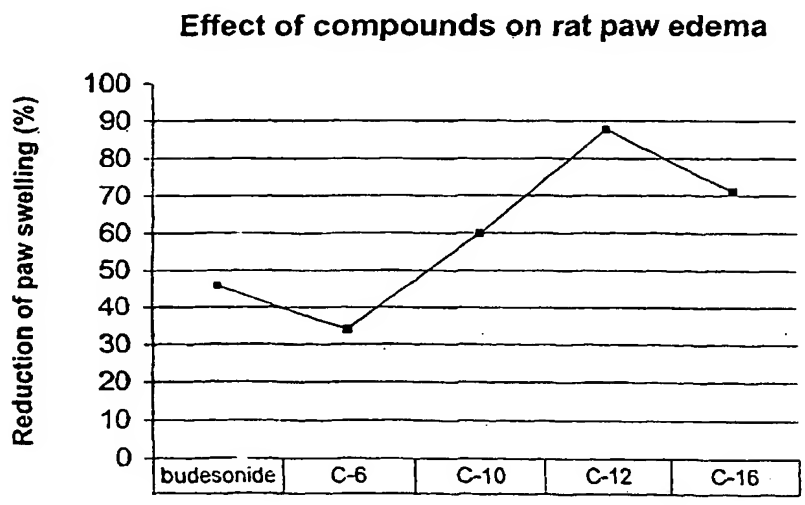
(75) Inventors/Applicants (*for US only*): GROVER, Paul [US/US]; 4 Warwick Road, Franklin, MA 02038 (US). JONES, Steve [US/US]; 10 Ragged Hill Road, Milford, MA 01757 (US). SENANAYAKE, Chris, H. [US/US]; 12 Isabel's Way, Brookfield, CT 06804 (US). CURRIE, Mark, G. [US/US]; 18 Hall Avenue, Sterling, MA 01564 (US). FANG, Q., Kevin [US/US]; 35 Atwood Street, Wellesley, MA 02181 (US).

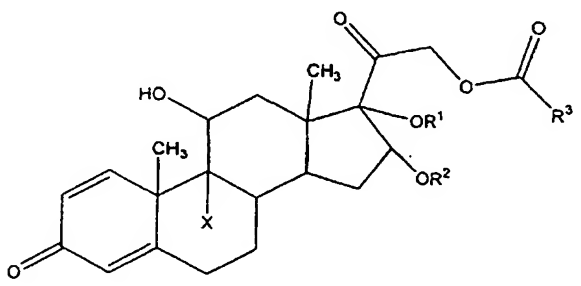
(74) Agent: HANSEN, Philip E.; HESLIN ROTHENBERG FARLEY & MESITI P.C., 5 Columbia Circle, Albany, NY 12203 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

[Continued on next page]

(54) Title: CARBONATE AND CARBAMATE MODIFIED FORMS OF GLUCOCORTICOIDS





(57) Abstract: Carbonates and carbamates of the formula and related steroid carbonates and carbamates are disclosed. The compounds are useful for treating rhinitis and asthma, particularly by inhalation, and for treating inflammation, particularly by local or topical administration.

WO 2003/070745 A3

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *with amended claims*

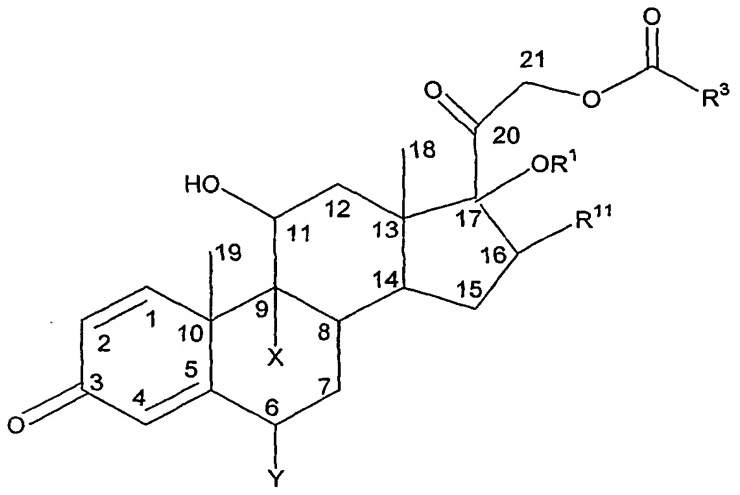
(88) Date of publication of the international search report: 20 November 2003

Date of publication of the amended claims: 19 February 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

AMENDED CLAIMS
[received by the International Bureau on 07 November 2003 (07.11.03);
original claims 1, 5 and 21 replaced by amended claims 1, 5 and 21;
remaining claims unchanged]

1. A compound of Formula I:



(I)

wherein

R^1 and R^2, independently for each occurrence, represent lower alkyl or lower acyl, or taken together R^1 and R^2 form a substituted or unsubstituted ketal;

R^3 is $-OR^4$ or $-NR^5R^6$;

R^4 is chosen from C_7 to C_{24} hydrocarbon, -(C_7 to C_{24} hydrocarbon)-COOH and -(C_7 to C_{24} hydrocarbon)-NR^9R^{10};

R^5 is hydrogen or C_7 to C_{24} hydrocarbon;

R^6 is C_7 to C_{24} hydrocarbon;

R^9 is hydrogen or C_1 to C_{17} hydrocarbon;

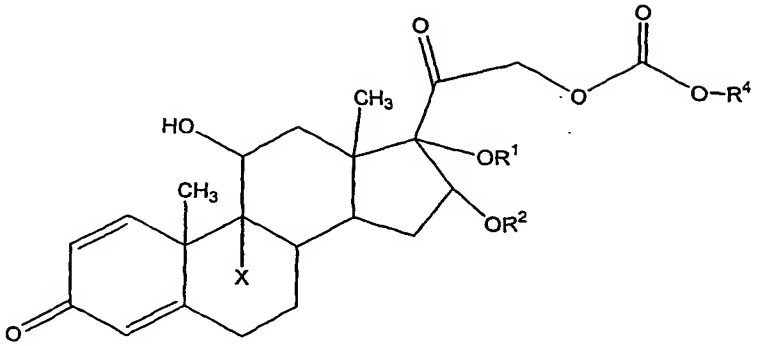
R^{10} is hydrogen or C_1 to C_{17} hydrocarbon;

R^{11} is $-OR^2$; and

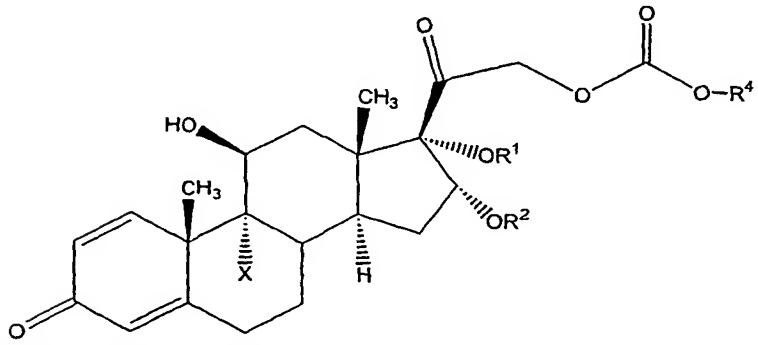
X and Y are independently hydrogen or halogen.

AMENDED SHEET (ARTICLE 19)

2. A compound according to claim 1of formula:

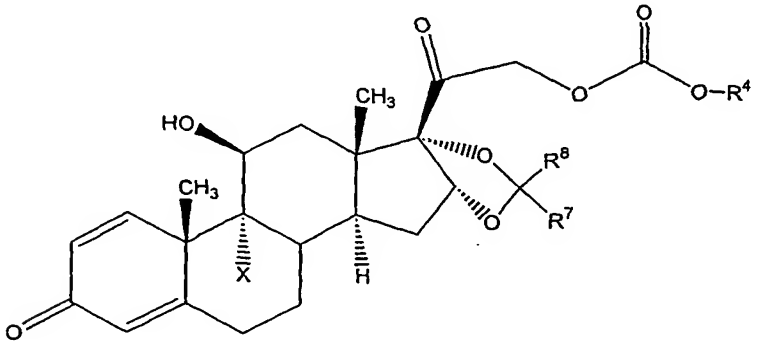


3. A compound according to claim 2 of formula:



wherein X is hydrogen or fluorine.

4. A compound according to claim 3 of formula

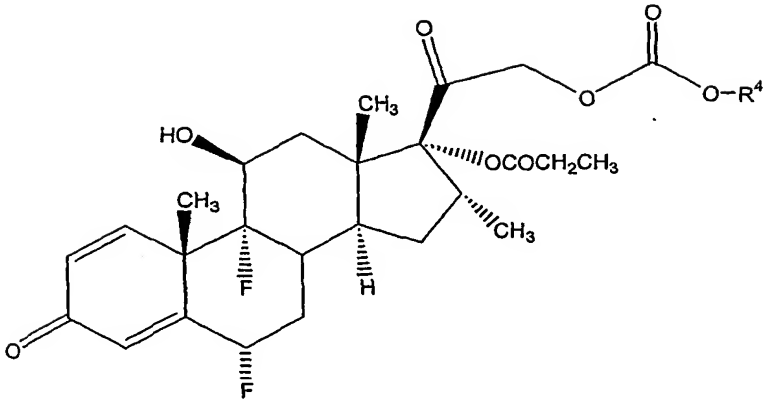


wherein

R^7 is hydrogen or lower alkyl; and

R^8 is lower alkyl.

5. A compound of formula



6. A compound according to any of claims 1 to 5 wherein R^4 is C_{11} to C_{14} alkyl.

7. A compound according to any of claims 1 to 5 wherein R^4 is C_{11} to C_{18} alkyl.

8. A compound according to any of claims 1 to 5 wherein R^4 is C_{12} to C_{24} alkyl.

9. A compound according to any of claims 1 to 5 wherein R^4 is C_{12} to C_{20} alkyl.

10. A compound according to any of claims 1 to 5 wherein R^4 is C_7 to C_{24} alkyl.

11. A compound according to any of claims 1 to 5 wherein R^4 is C_8 to C_{24} alkyl.

12. A compound according to any of claims 1 to 5 wherein R^4 is C_9 to C_{24} alkyl.

13. A compound according to any of claims 1 to 5 wherein R^4 is C_{10} to C_{24} alkyl.

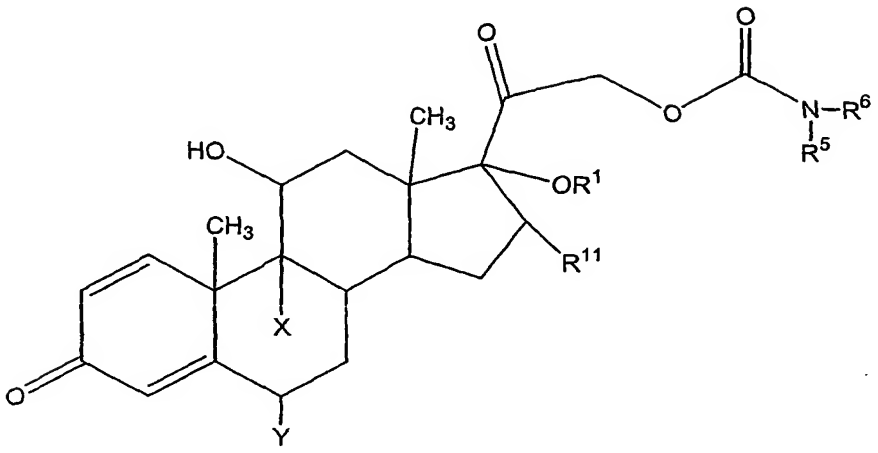
14. A compound according to any of claims 1 to 5 wherein R^4 is C_{11} to C_{24} alkyl.

15. A compound according to any of claims 1 to 5 wherein R^4 is C_8 to C_{18} alkyl.

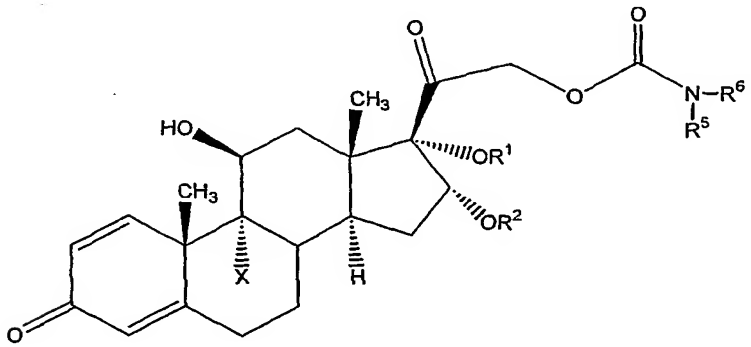
16. A compound according to any of claims 1 to 5 wherein R^4 is C_{10} to C_{16} alkyl.

17. A compound according to any of claims 1 to 5 wherein R^4 is C_8 to C_{20} alkyl.

18. A compound according to claim 1of formula:

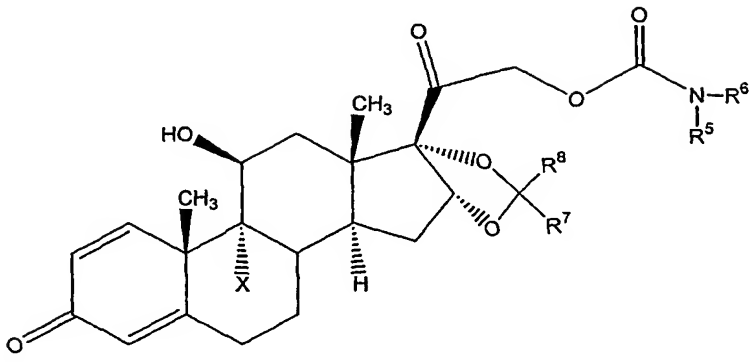


19. A compound according to claim 18 of formula:



AMENDED SHEET (ARTICLE 19)

20. A compound according to claim 19 of formula

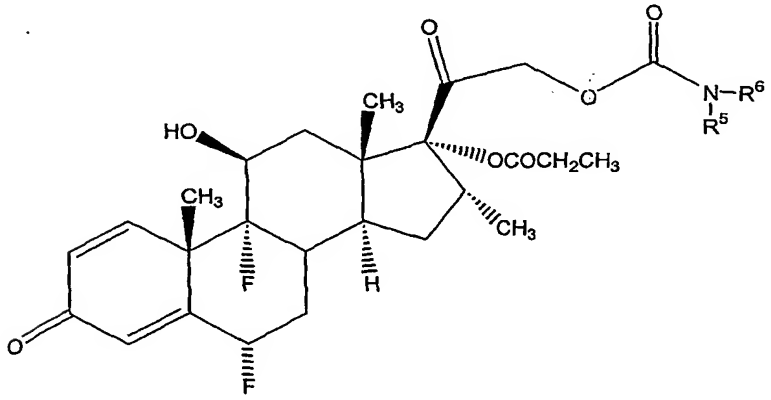


wherein

R^7 is hydrogen or lower alkyl; and

R^8 is lower alkyl.

21. A compound of formula



22. A compound according to any of claims 18 to 21 wherein R^5 is hydrogen or lower alkyl.

23. A compound according to any of claims 18 to 21 wherein R^6 is C_{11} to C_{14} alkyl.

24. A compound according to any of claims 18 to 21 wherein R^6 is C_{11} to C_{18} alkyl.

25. A compound according to any of claims 18 to 21 wherein R^6 is C_{12} to C_{24} alkyl.

26. A compound according to any of claims 18 to 21 wherein R^6 is C_{12} to C_{20} alkyl.

27. A compound according to any of claims 18 to 21 wherein R^6 is C_7 to C_{24} alkyl.

28. A compound according to any of claims 18 to 21 wherein R^6 is C_8 to C_{24} alkyl.

29. A compound according to any of claims 18 to 21 wherein R^6 is C_9 to C_{24} alkyl.

30. A compound according to any of claims 18 to 21 wherein R^6 is C_{10} to C_{24} alkyl.

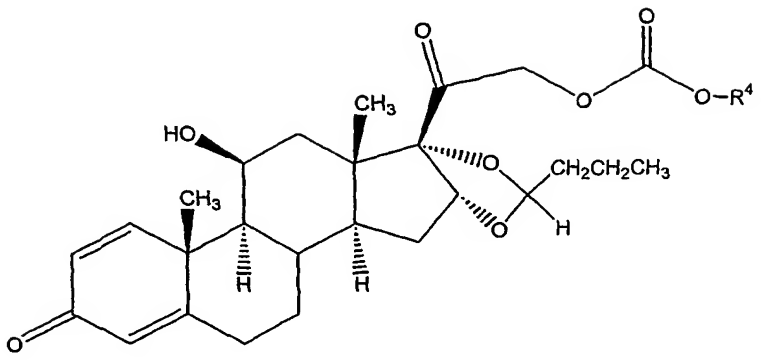
31. A compound according to any of claims 18 to 21 wherein R^6 is C_{11} to C_{24} alkyl.

32. A compound according to any of claims 18 to 21 wherein R^6 is C_8 to C_{18} alkyl.

33. A compound according to any of claims 18 to 21 wherein R^6 is C_{10} to C_{16} alkyl.

34. A compound according to any of claims 18 to 21 wherein R^6 is C_8 to C_{20} alkyl.

35. A compound according to claim 3 of formula



wherein R^4 is n-dodecyl.

36. A method for treating rhinitis comprising administering the compound of any of claims 1-35.

37. A method for treating asthma comprising administering the compound of any of claims 1-35.

38. A method according to either of claims 36 or 37 wherein said compound is administered by inhalation.

39. A method for treating a disorder chosen from osteoarthritis, bursitis, epicondylitis, tenosynovitis, lichen simplex chronicus, granuloma annulare, lichen planus, keloids, alopecia areata, discoid lupus erythematosus, localised neurodermatitis, cystic acne, granuloma annulare, nummular and dyshydrotic eczema, hypertrophic scars and macular degeneration comprising administering the compound of any of claims 1-35.

40. A pharmaceutical formulation for inhalation comprising a compound according to any of claims 1-35 and a pharmaceutically acceptable fluid for suspension or solution.

41. A pharmaceutical formulation for inhalation according to claim 40 additionally comprising a propellant.

42. A pharmaceutical formulation for topical application comprising a compound according to any of claims 1-35 and a pharmaceutically acceptable carrier for topical or transdermal application.